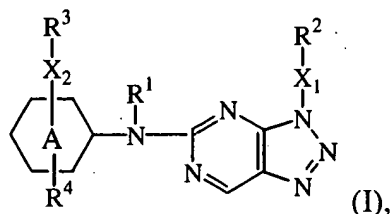


Claims

1. A compound of formula



a *N*-oxide, a pharmaceutically acceptable addition salt, a quaternary amine and a stereochemically isomeric form thereof, wherein

ring A represents phenyl, pyridyl, pyrimidinyl, pyridazinyl or pyrazinyl;

R^1 represents hydrogen; aryl; formyl; C_{1-6} alkylcarbonyl; C_{1-6} alkyl;

C_{1-6} alkyloxycarbonyl; C_{1-6} alkyl substituted with formyl, C_{1-6} alkylcarbonyl,

C_{1-6} alkyloxycarbonyl, C_{1-6} alkylcarbonyloxy; or C_{1-6} alkyloxy C_{1-6} alkylcarbonyl

optionally substituted with C_{1-6} alkyloxycarbonyl;

X_1 represents a direct bond; $-(CH_2)_{n3}-$ or $-(CH_2)_{n4}-X_{1a}-X_{1b}-$;

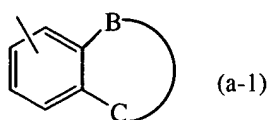
with n_3 representing an integer with value 1, 2, 3 or 4;

with n_4 representing an integer with value 1 or 2;

with X_{1a} representing O, C(=O) or NR^5 ; and

with X_{1b} representing a direct bond or C_{1-2} alkyl;

R^2 represents C_{3-7} cycloalkyl; phenyl; a 4, 5, 6- or 7-membered monocyclic heterocycle containing at least one heteroatom selected from O, S or N; benzoxazolyl or a radical of formula



wherein $-B-C-$ represents a bivalent radical of formula

$-CH_2-CH_2-CH_2-$ (b-1);

$-CH_2-CH_2-CH_2-CH_2-$ (b-2);

$-X_3-CH_2-CH_2-(CH_2)_n-$ (b-3);

$-X_3-CH_2-(CH_2)_n-X_3-$ (b-4);

$-X_3-(CH_2)_n-CH=CH-$ (b-5);

$-CH=N-X_3-$ (b-6);

with X_3 representing O or NR^5 ;

n representing an integer with value 0, 1, 2 or 3;

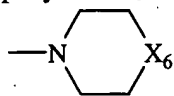
n' representing an integer with value 0 or 1;

wherein said R^2 substituent, where possible, may optionally be substituted with at least one substituent selected from halo; hydroxy; C_{1-6} alkyl optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, C_{1-4} alkyloxy,

- C₁₋₄alkyloxyC₁₋₄alkyloxy, C₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonyl, C₁₋₄alkylcarbonyloxy, NR⁶R⁷, -C(=O)-NR⁶R⁷, -NR⁵-C(=O)-NR⁶R⁷, -S(=O)_{n1}-R⁸ or -NR⁵-S(=O)_{n1}-R⁸; C₂₋₆alkenyl or C₂₋₆alkynyl, each optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, C₁₋₄alkyloxy, C₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonyl, C₁₋₄alkylcarbonyloxy, NR⁶R⁷, -C(=O)-NR⁶R⁷, -NR⁵-C(=O)-NR⁶R⁷, -S(=O)_{n1}-R⁸ or -NR⁵-S(=O)_{n1}-R⁸; polyhalo-C₁₋₆alkyl optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, C₁₋₄alkyloxy, C₁₋₄alkyloxyC₁₋₄alkyloxy, C₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonyl, C₁₋₄alkylcarbonyloxy, NR⁶R⁷, -C(=O)-NR⁶R⁷, -NR⁵-C(=O)-NR⁶R⁷, -S(=O)_{n1}-R⁸ or -NR⁵-S(=O)_{n1}-R⁸; C₁₋₆alkyloxy optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, C₁₋₄alkyloxy, C₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonyl, C₁₋₄alkylcarbonyloxy, NR⁶R⁷, -C(=O)-NR⁶R⁷, -NR⁵-C(=O)-NR⁶R⁷, -S(=O)_{n1}-R⁸ or -NR⁵-S(=O)_{n1}-R⁸; polyhaloC₁₋₆alkyloxy optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, C₁₋₄alkyloxy, C₁₋₄alkyloxyC₁₋₄alkyloxy, C₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonyl, C₁₋₄alkylcarbonyloxy, NR⁶R⁷, -C(=O)-NR⁶R⁷, -NR⁵-C(=O)-NR⁶R⁷, -S(=O)_{n1}-R⁸ or -NR⁵-S(=O)_{n1}-R⁸; C₁₋₆alkylthio; polyhaloC₁₋₆alkylthio; C₁₋₆alkyloxycarbonyl; C₁₋₆alkylcarbonyloxy; C₁₋₆alkylcarbonyl; polyhaloC₁₋₆alkylcarbonyl; cyano; carboxyl; aryloxy; arylthio; arylcarbonyl; arylC₁₋₄alkyl; arylC₁₋₄alkyloxy; NR⁶R⁷; C(=O)NR⁶R⁷; -NR⁵-C(=O)-NR⁶R⁷; -NR⁵-C(=O)-R⁵; -S(=O)_{n1}-R⁸; -NR⁵-S(=O)_{n1}-R⁸; -S-CN; -NR⁵-CN; oxazolyl optionally substituted with C₁₋₄alkyl; imidazolyl optionally substituted with C₁₋₄alkyl; or
- $$-(\text{CH}_2)_{n2}-\text{X}_4-(\text{CH}_2)_{n2}-\text{N} \begin{array}{c} \diagup \quad \diagdown \\ \text{---} \quad \text{---} \\ \diagdown \quad \diagup \end{array} \text{X}_5$$
- with n2 representing an integer with value 0, 1, 2, 3 or 4;
with X₄ representing O, NR⁵ or a direct bond;
with X₅ representing O, CH₂, CHOH, CH-N(R₅)₂, NR⁵ or N-C(=O)-C₁₋₄alkyl;
X₂ represents a direct bond; -NR¹-; -NR¹-(CH₂)_{n3}-; -O-; -O-(CH₂)_{n3}-; -C(=O)-; -C(=O)-(CH₂)_{n3}-; -C(=O)-NR⁵-(CH₂)_{n3}-; -C(=S)-; -S-; -S(=O)_{n1}-; -(CH₂)_{n3}-; -(CH₂)_{n4}-X_{1a}-X_{1b}-; -X_{1a}-X_{1b}-(CH₂)_{n4}-; -S(=O)_{n1}-NR⁵-(CH₂)_{n3}-NR⁵-; or -S(=O)_{n1}-NR⁵-(CH₂)_{n3}-;
R³ represents a 5-or 6-membered monocyclic heterocycle containing at least one heteroatom selected from O, S or N, or a 9-or 10-membered bicyclic heterocycle containing at least one heteroatom selected from O, S or N, wherein said R³ substituent, where possible, may optionally be substituted with at least one substituent selected from halo; hydroxy; C₁₋₆alkyl optionally substituted with at least

- one substituent selected from hydroxy, cyano, carboxyl, C₁₋₄alkyloxy, C₁₋₄alkyloxyC₁₋₄alkyloxy, C₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonyl, C₁₋₄alkylcarbonyloxy, NR⁶R⁷, -C(=O)-NR⁶R⁷, -NR⁵-C(=O)-NR⁶R⁷, -S(=O)_{n1}-R⁸ or -NR⁵-S(=O)_{n1}-R⁸; C₂₋₆alkenyl or C₂₋₆alkynyl, each optionally substituted with at
- 5 least one substituent selected from hydroxy, cyano, carboxyl, C₁₋₄alkyloxy, C₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonyl, C₁₋₄alkylcarbonyloxy, NR⁶R⁷, -C(=O)-NR⁶R⁷, -NR⁵-C(=O)-NR⁶R⁷, -S(=O)_{n1}-R⁸ or -NR⁵-S(=O)_{n1}-R⁸; polyhaloC₁₋₆alkyl; C₁₋₆alkyloxy optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, C₁₋₄alkyloxy, C₁₋₄alkylcarbonyl,
- 10 C₁₋₄alkyloxycarbonyl, C₁₋₄alkylcarbonyloxy, NR⁶R⁷, -C(=O)-NR⁶R⁷, -NR⁵-C(=O)-NR⁶R⁷, -S(=O)_{n1}-R⁸ or -NR⁵-S(=O)_{n1}-R⁸; polyhaloC₁₋₆alkyloxy; C₁₋₆alkylthio; polyhaloC₁₋₆alkylthio; C₁₋₆alkyloxycarbonyl; C₁₋₆alkylcarbonyloxy; C₁₋₆alkylcarbonyl; polyhaloC₁₋₆alkylcarbonyl; cyano; carboxyl; NR⁶R⁷; C(=O)NR⁶R⁷; -NR⁵-C(=O)-NR⁶R⁷; -NR⁵-C(=O)-R⁵; -S(=O)_{n1}-R⁸; -NR⁵-S(=O)_{n1}-R⁸; -S-CN;
- 15 -NR⁵-CN; or $-(CH_2)_{n2}-X_4-(CH_2)_{n2}-N \begin{array}{c} \diagup \diagdown \\ \diagdown \diagup \end{array} \begin{array}{c} X_5 \\ X_5 \end{array}$; and in case R³ represents a saturated or a partially saturated 5- or 6-membered monocyclic heterocycle containing at least one heteroatom selected from O, S or N, said R³ may also be substituted with at least one oxo;
- 20 R⁴ represents hydrogen; halo; hydroxy; C₁₋₄alkyl optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, C₁₋₄alkyloxy, C₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonyl, C₁₋₄alkylcarbonyloxy, NR⁹R¹⁰, -C(=O)-NR⁹R¹⁰, -NR⁵-C(=O)-NR⁹R¹⁰, -S(=O)_{n1}-R¹¹ or -NR⁵-S(=O)_{n1}-R¹¹; C₂₋₄alkenyl or C₂₋₄alkynyl, each optionally substituted with at least one substituent selected from hydroxy,
- 25 cyano, carboxyl, C₁₋₄alkyloxy, C₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonyl, C₁₋₄alkylcarbonyloxy, NR⁹R¹⁰, -C(=O)-NR⁹R¹⁰, -NR⁵-C(=O)-NR⁹R¹⁰, -S(=O)_{n1}-R¹¹ or -NR⁵-S(=O)_{n1}-R¹¹; polyhaloC₁₋₃alkyl; C₁₋₄alkyloxy optionally substituted with carboxyl; polyhaloC₁₋₃alkyloxy; C₁₋₄alkylthio; polyhaloC₁₋₃alkylthio; C₁₋₄alkyloxycarbonyl; C₁₋₄alkylcarbonyloxy; C₁₋₄alkylcarbonyl;
- 30 polyhaloC₁₋₄alkylcarbonyl; nitro; cyano; carboxyl; NR⁹R¹⁰; C(=O)NR⁹R¹⁰; -NR⁵-C(=O)-NR⁹R¹⁰; -NR⁵-C(=O)-R⁵; -S(=O)_{n1}-R¹¹; -NR⁵-S(=O)_{n1}-R¹¹; -S-CN; or -NR⁵-CN;
- R⁵ represents hydrogen, C₁₋₄alkyl or C₂₋₄alkenyl;
- R⁶ and R⁷ each independently represent hydrogen; cyano; C₁₋₆alkylcarbonyl optionally
- 35 substituted with C₁₋₄alkyloxy or carboxyl; C₁₋₆alkyloxycarbonyl; C₃₋₇cycloalkylcarbonyl; adamantanylcabonyl; C₁₋₄alkyloxyC₁₋₄alkyl;

C₁₋₄alkyl substituted with C₁₋₄alkyl-NR⁵-; C₁₋₆alkyl optionally substituted with at least one substituent selected from halo, hydroxy, cyano, carboxyl, C₁₋₄alkyloxy, polyhaloC₁₋₄alkyl, C₁₋₄alkyloxyC₁₋₄alkyloxy, NR^{6a}R^{7a}, C(=O)NR^{6a}R^{7a} or



; with X₆ representing O, CH₂, CHOH, CH-N(R₅)₂, NR⁵ or

5 N-C(=O)-C₁₋₄alkyl;

R^{6a} and R^{7a} each independently represent hydrogen; C₁₋₄alkyl or C₁₋₄alkylcarbonyl;

R⁸ represents C₁₋₄alkyl optionally substituted with hydroxy; polyhaloC₁₋₄alkyl or NR⁶R⁷;

R⁹ and R¹⁰ each independently represent hydrogen; C₁₋₆alkyl; cyano; C₁₋₆alkylcarbonyl;

10 C₁₋₄alkyloxyC₁₋₄alkyl; or C₁₋₄alkyl substituted with C₁₋₄alkyl-NR⁵-;

R¹¹ represents C₁₋₄alkyl or NR⁹R¹⁰;

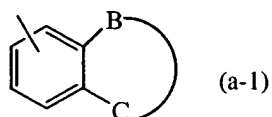
n₁ represents an integer with value 1 or 2;

aryl represents phenyl or phenyl substituted with at least one substituent selected from halo, C₁₋₆alkyl, C₃₋₇cycloalkyl, C₁₋₆alkyloxy, cyano, nitro, polyhaloC₁₋₆alkyl or

15 polyhaloC₁₋₆alkyloxy.

2. A compound according to claim 1 wherein

R² represents C₃₋₇cycloalkyl; phenyl or a 4, 5, 6- or 7-membered monocyclic heterocycle containing at least one heteroatom selected from O, S or N; or a radical
20 of formula



(a-1)

wherein -B-C- represents a bivalent radical of formula

-CH₂-CH₂-CH₂- (b-1);

-CH₂-CH₂-CH₂-CH₂- (b-2);

25 -X₃-CH₂-CH₂-(CH₂)_n- (b-3);

-X₃-CH₂-(CH₂)_n-X₃- (b-4);

-X₃-(CH₂)_n'-CH=CH- (b-5);

with X₃ representing O or NR⁵;

n representing an integer with value 0, 1, 2 or 3;

30 n' representing an integer with value 0 or 1;

wherein said R² substituent, where possible, may optionally be substituted with at least one substituent selected from halo; hydroxy; C₁₋₆alkyl optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, C₁₋₄alkyloxy, C₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonyl, C₁₋₄alkylcarbonyloxy, NR⁶R⁷,

-C(=O)-NR⁶R⁷, -NR⁵-C(=O)-NR⁶R⁷, -S(=O)_{n1}-R⁸ or -NR⁵-S(=O)_{n1}-R⁸; C₂₋₆alkenyl or C₂₋₆alkynyl, each optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, C₁₋₄alkyloxy, C₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonyl, C₁₋₄alkylcarbonyloxy, NR⁶R⁷, -C(=O)-NR⁶R⁷, -NR⁵-C(=O)-NR⁶R⁷, -S(=O)_{n1}-R⁸ or -NR⁵-S(=O)_{n1}-R⁸; polyhaloC₁₋₆alkyl; C₁₋₆alkyloxy optionally substituted with carboxyl; polyhaloC₁₋₆alkyloxy; C₁₋₆alkylthio; polyhaloC₁₋₆alkylthio; C₁₋₆alkyloxycarbonyl; C₁₋₆alkylcarbonyloxy; C₁₋₆alkylcarbonyl; polyhaloC₁₋₆alkylcarbonyl; cyano; carboxyl; NR⁶R⁷; C(=O)NR⁶R⁷; -NR⁵-C(=O)-NR⁶R⁷; -NR⁵-C(=O)-R⁵; -S(=O)_{n1}-R⁸; -NR⁵-S(=O)_{n1}-R⁸; -S-CN; -NR⁵-CN; or

$$-(CH_2)_{n2}-X_4-(CH_2)_{n2}-N \begin{array}{c} \diagup \quad \diagdown \\ \diagdown \quad \diagup \end{array} X_5$$

with n₂ representing an integer with value 0, 1, 2, 3 or 4;

with X₄ representing O, NR⁵ or a direct bond;

with X₅ representing O or NR⁵;

X₂ represents a direct bond; -NR¹-; -O-; -C(=O)-; -C(=S)-; -S-; -S(=O)_{n1}-; -(CH₂)_{n3}-; or -(CH₂)_{n4}-X_{1a}-X_{1b}-;

R³ represents a 5- or 6-membered monocyclic heterocycle containing at least one heteroatom selected from O, S or N, wherein said R³ substituent, where possible, may optionally be substituted with at least one substituent selected from halo; hydroxy; C₁₋₆alkyl optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, C₁₋₄alkyloxy, C₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonyl, C₁₋₄alkylcarbonyloxy, NR⁶R⁷, -C(=O)-NR⁶R⁷, -NR⁵-C(=O)-NR⁶R⁷, -S(=O)_{n1}-R⁸ or -NR⁵-S(=O)_{n1}-R⁸; C₂₋₆alkenyl or C₂₋₆alkynyl, each optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, C₁₋₄alkyloxy, C₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonyl, C₁₋₄alkylcarbonyloxy, NR⁶R⁷, -C(=O)-NR⁶R⁷, -NR⁵-C(=O)-NR⁶R⁷, -S(=O)_{n1}-R⁸ or -NR⁵-S(=O)_{n1}-R⁸; polyhaloC₁₋₆alkyl; C₁₋₆alkyloxy optionally substituted with carboxyl; polyhaloC₁₋₆alkyloxy; C₁₋₆alkylthio; polyhaloC₁₋₆alkylthio; C₁₋₆alkyloxycarbonyl; C₁₋₆alkylcarbonyloxy; C₁₋₆alkylcarbonyl; polyhaloC₁₋₆alkylcarbonyl; cyano; carboxyl; NR⁶R⁷; C(=O)NR⁶R⁷; -NR⁵-C(=O)-NR⁶R⁷; -NR⁵-C(=O)-R⁵;

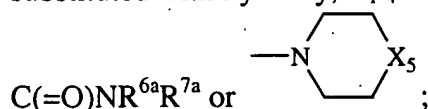
-S(=O)_{n1}-R⁸; -NR⁵-S(=O)_{n1}-R⁸; -S-CN; -NR⁵-CN; or

$$-(CH_2)_{n2}-X_4-(CH_2)_{n2}-N \begin{array}{c} \diagup \quad \diagdown \\ \diagdown \quad \diagup \end{array} X_5$$

and in case R³ represents a saturated 5- or 6-membered monocyclic heterocycle containing at least one heteroatom selected from O, S or N, said R³ may also be substituted with at least one oxo;

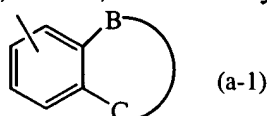
R⁵ represents hydrogen or C₁₋₄alkyl;

R^6 and R^7 each independently represent hydrogen; cyano; C_{1-6} alkylcarbonyl; C_{1-4} alkyloxy C_{1-4} alkyl; C_{1-4} alkyl substituted with C_{1-4} alkyl- NR^5 -; C_{1-6} alkyl optionally substituted with hydroxy, C_{1-4} alkyloxy, C_{1-4} alkyloxy C_{1-4} alkyloxy, $NR^{6a}R^{7a}$,



5 R^8 represents C_{1-4} alkyl, polyhalo C_{1-4} alkyl or NR^6R^7 .

3. A compound as claimed in claim 1 wherein ring A represents phenyl; R^1 represents hydrogen or C_{1-6} alkyl; X_1 represents a direct bond or $-(CH_2)_{n3}$ -; R^2 represents C_{3-7} cycloalkyl; phenyl; a 6-membered monocyclic heterocycle containing at least one
10 heteroatom selected from O, S or N; benzoxazolyl; or a radical of formula



wherein $-B-C-$ represents a bivalent radical of formula

$-CH_2-CH_2-CH_2-$ (b-1);

$-X_3-CH_2-(CH_2)_n-X_3-$ (b-4);

15 $-CH=N-X_3-$ (b-6);

with X_3 representing O or NR^5 ;

n representing an integer with value 1;

wherein said R^2 substituent, where possible, may optionally be substituted with at least one substituent, in particular with 1 or 2 substituents selected from halo; C_{1-6} alkyl
20 optionally substituted with at least one substituent selected from hydroxy, cyano, C_{1-4} alkyloxy, C_{1-4} alkyloxy C_{1-4} alkyloxy, NR^6R^7 or $-C(=O)-NR^6R^7$; polyhalo C_{1-6} alkyl; C_{1-6} alkyloxy optionally substituted with C_{1-4} alkyloxy; C_{1-6} alkylthio; C_{1-6} alkyl-oxycarbonyl; cyano; arylthio; aryloxy; arylcarbonyl; NR^6R^7 ; $C(=O)NR^6R^7$; $-S(=O)_{n1}-R^8$; or imidazolyl optionally substituted with C_{1-4} alkyl;
25 X_2 represents a direct bond; $-NR^1$ -; $-O-(CH_2)_{n3}$ -; $-C(=O)-$; $-C(=O)-NR^5-(CH_2)_{n3}$ -; $-(CH_2)_{n3}$ -; or $-S(=O)_{n1}-NR^5-(CH_2)_{n3}-NR^5$ -; R^3 represents a 5-or 6-membered monocyclic heterocycle containing at least one heteroatom selected from O, S or N, wherein said R^3 substituent, where possible, may optionally be substituted with at least one substituent selected from halo; hydroxy; C_{1-6} alkyl; or NR^6R^7 ; and in case R^3
30 represents a saturated or a partially saturated 5-or 6-membered monocyclic heterocycle containing at least one heteroatom selected from O, S or N, said R^3 may also be substituted with at least one oxo; R^4 represents hydrogen; nitro or carboxyl; R^5 represents hydrogen; R^6 and R^7 each independently represent hydrogen; cyano; C_{1-6} alkylcarbonyl optionally substituted with C_{1-4} alkyloxy; C_{1-6} alkyloxycarbonyl;

C₃₋₇cycloalkylcarbonyl; adamantanylcabonyl; or C₁₋₆alkyl; R⁸ represents NR⁶R⁷; n₁ represents an integer with value 2; aryl represents phenyl.

4. A compound as claimed in any one of claims 1 to 3 wherein ring A is phenyl; R¹ is
5 hydrogen; X₁ is a direct bond or -(CH₂)_{n3}-; R² is indanyl; 2,3-dihydro-1,4-
benzodioxanyl; phenyl optionally being substituted with 1 or 2 substituents
each independently being selected from C₁₋₆alkyl which may optionally be substituted
with hydroxy, cyano, C₁₋₄alkyloxy, C₁₋₄alkyloxyC₁₋₄alkyloxy, NR⁶R⁷ or C(=O)NR⁶R⁷;
C₁₋₆alkyloxy; halo; polyhaloC₁₋₆alkyl which may optionally be substituted with
10 hydroxy, cyano, C₁₋₄alkyloxy, C₁₋₄alkyloxyC₁₋₄alkyloxy, NR⁶R⁷ or C(=O)NR⁶R⁷;
cyano; NR⁶R⁷; C(=O)NR⁶R⁷; -S(=O)_{n1}-R⁸; X₂ is direct bond; -NR¹-; -O-(CH₂)_{n3}-;
-C(=O)-; -C(=O)-NR⁵-(CH₂)_{n3}-; or -(CH₂)_{n3}-; R³ is tetrazolyl; piperazinyl; imidazolyl;
oxazolyl; pyrimidinyl; thiazolyl; triazolyl; pyridyl; piperidinyl, pyrazinyl; pyrazolyl or
morpholinyl; said rings representing R³ may optionally be substituted with one
15 substituent selected from C₁₋₆alkyl; NR⁶R⁷; hydroxy; halo; and in case R³ represents a
saturated or a partially saturated ring system, said R³ may also be substituted with at
least one oxo; R⁴ is hydrogen; R⁶ and R⁷ each independently represent hydrogen;
cyano; C₁₋₆alkylcarbonyl optionally substituted with C₁₋₄alkyloxy;
C₁₋₆alkyloxycarbonyl; C₃₋₇cycloalkylcarbonyl; or C₁₋₆alkyl; R⁸ represents NR⁶R⁷.

20

5. A compound as claimed in any one of claims 1 to 4 wherein the R³ substituent is
linked to ring A in meta position compared to the NR¹ linker.

6. A compound as claimed in any one of claims 1 to 4 wherein the R³ substituent is
25 linked to ring A in para position compared to the NR¹ linker.

7. A compound as claimed in any one of claims 1 to 6 wherein the R³ substituent is an
optionally substituted saturated 6-membered monocyclic heterocycle containing at least
one heteroatom selected from O, S or N.

30

8. A compound as claimed in any one of claims 1 to 7 wherein X₁ represents a direct
bond.

9. A compound as claimed in any one of claims 1, 5 to 8 wherein R² represents
35 C₃₋₇cycloalkyl; phenyl; a 4, 5, 6- or 7-membered monocyclic heterocycle containing at
least one heteroatom selected from O, S or N; benzoxazolyl or a radical of formula (a-
1) wherein said R² substituent is substituted with at least one substituent selected from

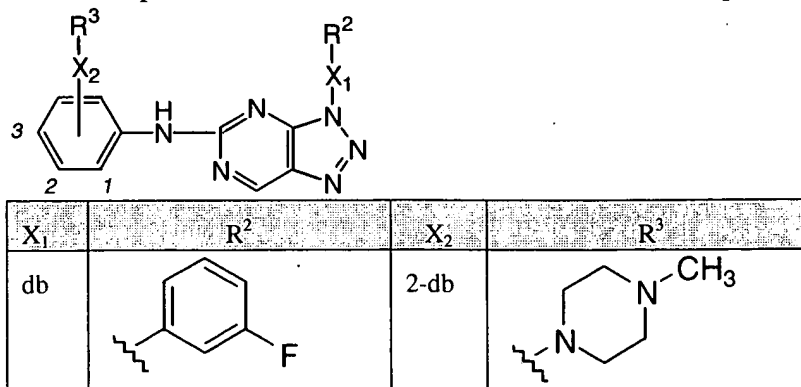
C₁₋₆alkyl substituted with NR⁶R⁷; C₂₋₆alkenyl or C₂₋₆alkynyl, each substituted with NR⁶R⁷; polyhaloC₁₋₆alkyl substituted with NR⁶R⁷; C₁₋₆alkyloxy substituted with NR⁶R⁷; polyhaloC₁₋₆alkyloxy substituted with NR⁶R⁷; or NR⁶R⁷.

- 5 10. A compound as claimed in any one of claims 1, 5, 6, 8 or 9 wherein R³ represents a 5- or 6-membered monocyclic heterocycle containing at least one heteroatom selected from O, S or N, or a 9- or 10-membered bicyclic heterocycle containing at least one heteroatom selected from O, S or N, wherein said R³ substituent is substituted with at least one substituent selected from C₁₋₆alkyl substituted with NR⁶R⁷; C₂₋₆alkenyl or
10 C₂₋₆alkynyl, each substituted with NR⁶R⁷; C₁₋₆alkyloxy substituted with NR⁶R⁷; or NR⁶R⁷.

11. A compound as claimed in any one of claims 1, 5, 6, 7, 8 or 10 wherein R² represents C₃₋₇cycloalkyl; phenyl; a 4, 5, 6- or 7-membered monocyclic heterocycle
15 containing at least one heteroatom selected from O, S or N; benzoxazolyl or a radical of formula (a-1), wherein said R² substituent is substituted with at least one substituent selected from halo; polyhaloC₁₋₆alkyl optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, C₁₋₄alkyloxy, C₁₋₄alkyloxy-
C₁₋₄alkyloxy, C₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonyl, C₁₋₄alkylcarbonyloxy, NR⁶R⁷,
20 -C(=O)-NR⁶R⁷, -NR⁵-C(=O)-NR⁶R⁷, -S(=O)_{n1}-R⁸ or -NR⁵-S(=O)_{n1}-R⁸; polyhalo-
C₁₋₆alkyloxy optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, C₁₋₄alkyloxy, C₁₋₄alkyloxyC₁₋₄alkyloxy, C₁₋₄alkylcarbonyl,
C₁₋₄alkyloxycarbonyl, C₁₋₄alkylcarbonyloxy, NR⁶R⁷, -C(=O)-NR⁶R⁷,
-NR⁵-C(=O)-NR⁶R⁷, -S(=O)_{n1}-R⁸ or -NR⁵-S(=O)_{n1}-R⁸.

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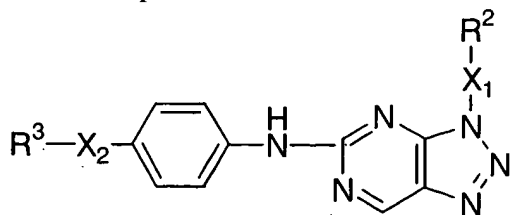
12. A compound as claimed in claim 1 wherein the compound is selected from



X_1	R^2	X_2	R^3
db		2-db	
db		2-db	
db		2-db	
db		2-db	
db		3-db	
db		2-db	
db		3-NH	
db		2-db	
db		3-db	

a *N*-oxide, a pharmaceutically acceptable addition salt, a quaternary amine and a stereochemically isomeric form thereof.

13. A compound as claimed in claim 1 wherein the compound is selected from



X_1	R^2	X_2-R^3
db		
db		
db		
db		
db		
db		
db		

a *N*-oxide, a pharmaceutically acceptable addition salt, a quaternary amine and a stereochemically isomeric form thereof.

5 14. A compound as claimed in any one of claims 1 to 13 for use as a medicine.

15. The use of a compound as defined in any one of claims 1 to 13 for the manufacture of a medicament for the prevention or the treatment of diseases mediated through GSK3.

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16. The use of a compound as defined in any one of claims 1 to 13 for the manufacture of a medicament for the prevention or the treatment of bipolar disorder (in particular manic depression), diabetes, Alzheimer's disease, leukopenia, FTDP-17 (Fronto-temporal dementia associated with Parkinson's disease), cortico-basal degeneration, progressive supranuclear palsy, multiple system atrophy, Pick's disease, Niemann Pick's disease type C, Dementia Pugilistica, dementia with tangles only, dementia with

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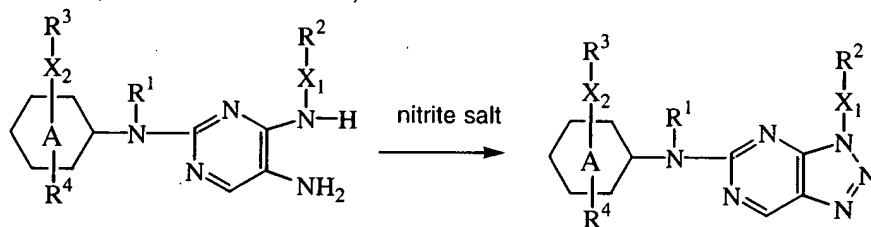
tangles and calcification, Downs syndrome, myotonic dystrophy, Parkinsonism-dementia complex of Guam, aids related dementia, Postencephalic Parkinsonism, prion diseases with tangles, subacute sclerosing panencephalitis, frontal lobe degeneration (FLD), argyrophilic grains disease, subacute sclerotizing panencephalitis (SSPE) (late
5 complication of viral infections in the central nervous system), inflammatory diseases, depression, cancer, dermatological disorders, neuroprotection, schizophrenia, pain.

17. The use of a compound as claimed in claim 16 for the prevention or the treatment
of Alzheimer's disease; diabetes; cancer; inflammatory diseases; bipolar disorder;
10 depression; pain.

18. A pharmaceutical composition comprising a pharmaceutically acceptable carrier
and as active ingredient a therapeutically effective amount of a compound as claimed in
any one of claims 1 to 13.

19. A process for preparing a pharmaceutical composition as claimed in claim 18
characterized in that a therapeutically effective amount of a compound as claimed in
any one of claims 1 to 13 is intimately mixed with a pharmaceutically acceptable
carrier.

20. A process for preparing a compound as claimed in claim 1, characterized by
a) cyclizing an intermediate of formula (II) in the presence of a nitrite salt, a suitable
solvent, and a suitable acid,

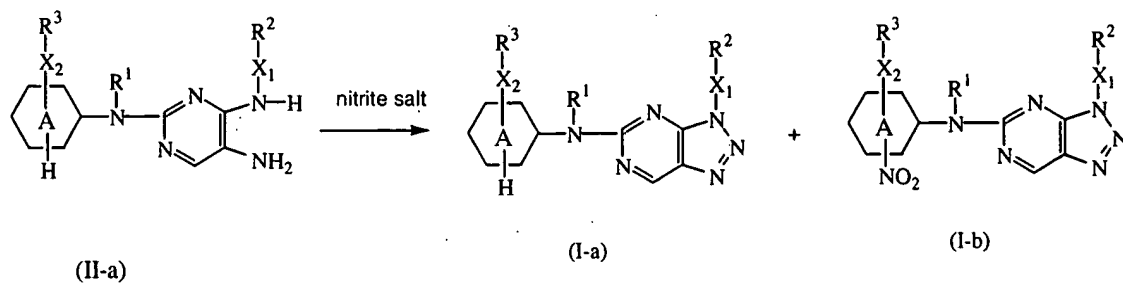


(II)

(I)

wherein ring A, R¹ to R⁴, X₁ and X₂ are as defined in claim 1;

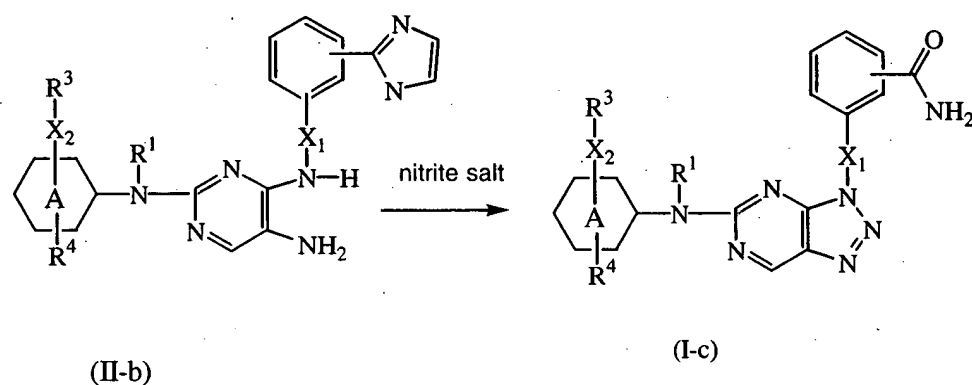
b) cyclizing an intermediate of formula (II-a) in the presence of a nitrite salt, a suitable
solvent, and a suitable acid,



wherein ring A, R¹ to R³, X₁ and X₂ are as defined in claim 1;

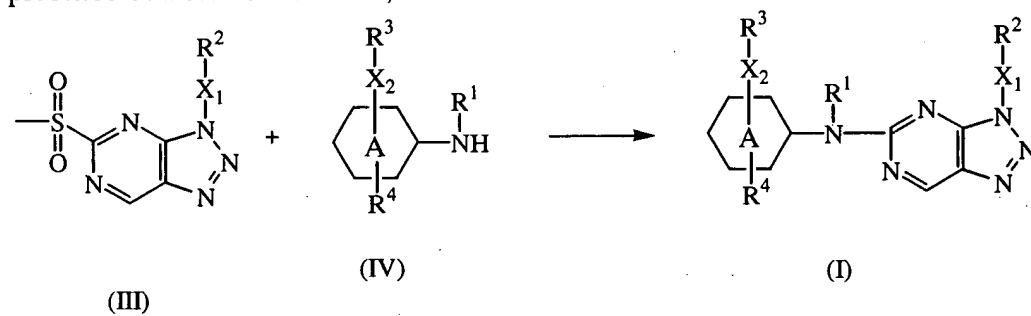
c) cyclizing an intermediate of formula (II-b) in the presence of a nitrite salt, a suitable solvent, and a suitable acid,

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wherein ring A, R¹, R³ and R⁴, X₁ and X₂ are as defined in claim 1;

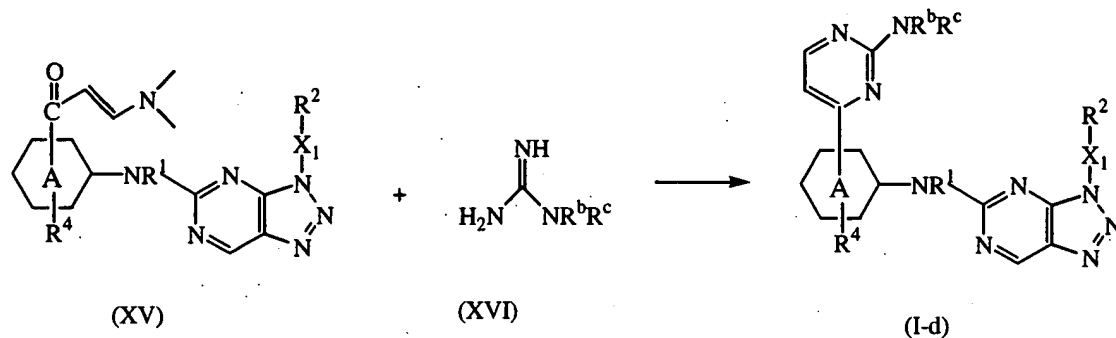
d) reacting an intermediate of formula (III) with an intermediate of formula (IV) in the presence of a suitable solvent,



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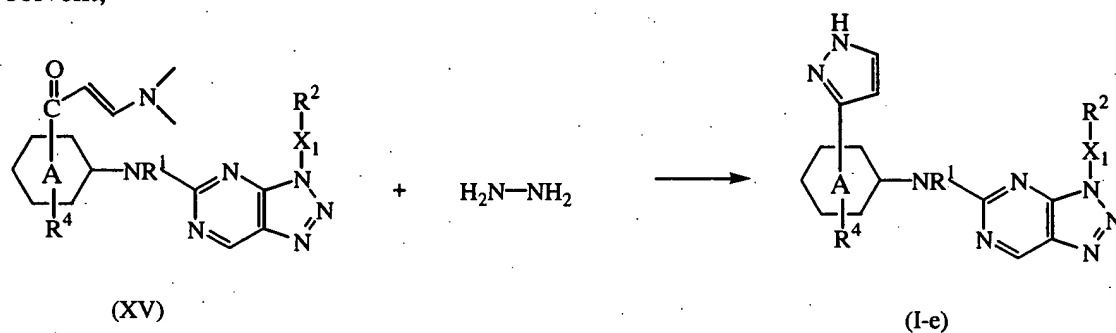
wherein ring A, R¹ to R⁴, X₁ and X₂ are as defined in claim 1;

e) reacting an intermediate of formula (XV) with an intermediate of formula (XVI), wherein R^b represents hydrogen, C₁₋₄alkyl or cyano, and R^c represents hydrogen or C₁₋₄alkyl, in the presence of a suitable solvent and a suitable salt



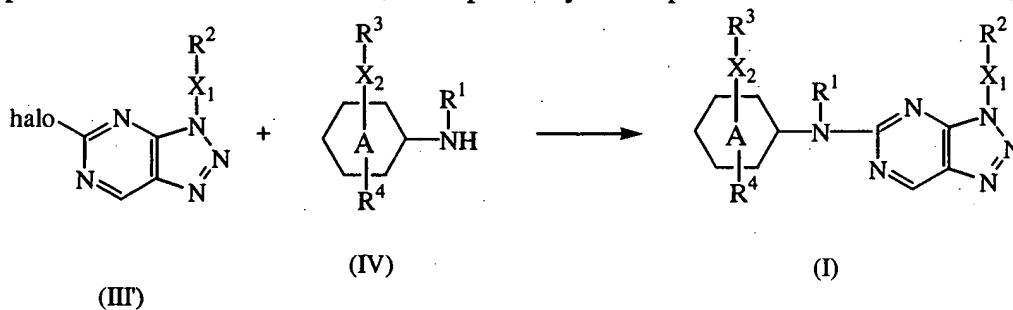
wherein ring A, R^1 , R^2 , R^4 and X_1 are as defined in claim 1;

f) reacting an intermediate of formula (XV) with hydrazine in the presence of a suitable solvent,



wherein ring A, R^1 , R^2 , R^4 and X_1 are as defined in claim 1;

g) reacting an intermediate of formula (III') with an intermediate of formula (IV) in the presence of a suitable solvent, and optionally in the presence of a suitable base,



wherein ring A, R^1 , R^2 , R^3 , R^4 , X_1 and X_2 are as defined in claim 1;

or, if desired, converting compounds of formula (I) into each other following art-known transformations, and further, if desired, converting the compounds of formula (I), into a therapeutically active non-toxic acid addition salt by treatment with an acid, or into a therapeutically active non-toxic base addition salt by treatment with a base, or conversely, converting the acid addition salt form into the free base by treatment with alkali, or converting the base addition salt into the free acid by treatment with acid; and, if desired, preparing stereochemically isomeric forms, quaternary amines or *N*-oxide forms thereof